

# Dynamic Contrast Enhanced (DCE)-MRI and Circulating Angiogenic Factors for Monitoring of Antiangiogenic Effect of Bevacizumab in Colorectal Cancer Liver Metastasis

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**Purpose:** This is a phase II clinical trial measuring correlation between vascular response assessed by Dynamic Contrast Enhanced (DCE)-MR imaging and plasma cytokines and angiogenic factors (CAFs) with clinical outcomes (progression free survival) of colorectal cancer liver metastasis (CRCLM) patients treated by Bevacizumab plus FOLFOX. The primary endpoint was progression-free survival (PFS). The secondary endpoints were correlation between tumor perfusion parameters of DCE-MRI and CAFs.

**Material and Methods:** Eligible patients were required to have histologically confirmed CRC with measurable liver metastasis with no prior chemotherapy. They received bevacizumab monotherapy followed by combined FOLFOX therapy. DCE-MRI ( $K^{\text{trans}}$  and  $i\text{AUC}_{60}$ ) was performed at baseline (1<sup>st</sup>), 3 days after bevacizumab monotherapy (2<sup>nd</sup>), and 3 days after combined therapy (3<sup>rd</sup>). Levels of CAFs (VEGF, PIGF, and IL-8) were assessed using multiplex-bead assays and enzyme-linked immunosorbent assays at the same days. PFS distributions were summarized by Kaplan-Meier methods and compared using log-rank tests. Written informed consent was obtained from each patient.

**Results:** 30 patients were enrolled (median PFS = 350 days). Compared to the baseline values,  $K^{\text{trans}}$ ,  $i\text{AUC}_{60}$ , VEGF, and PIGF on 3 days after bevacizumab monotherapy showed significant difference, but no difference on 3 days after combined therapy (Fig 1). When dichotomized at the median value of the baseline parameters of DCE-MRI and CAFs, only high  $i\text{AUC}_{60}$  were associated with a longer PFS ( $p = .002$ ) (Fig 2). More than 30% decrease in  $K^{\text{trans}}$  from 1<sup>st</sup> to 2<sup>nd</sup> day was associated with a longer PFS ( $p = .015$ ) (Fig 3). The changes in  $i\text{AUC}_{60}$  and CAFs did not correlate with PFS. Among the parameters of DCE-MRI and CAFs,  $K^{\text{trans}}$  and VEGF showed marginally significant correlation ( $p = .0623$ ).

**Conclusion:** Significant changes in DCE-MRI and CAFs on 3 day after bevacizumab monotherapy, not on 3 day after combined therapy, proved anti-angiogenic effect of bevacizumab monotherapy. Higher baseline  $i\text{AUC}_{60}$  and early reduction of  $K^{\text{trans}}$  could predict longer PFS in the patients with CRCLM.

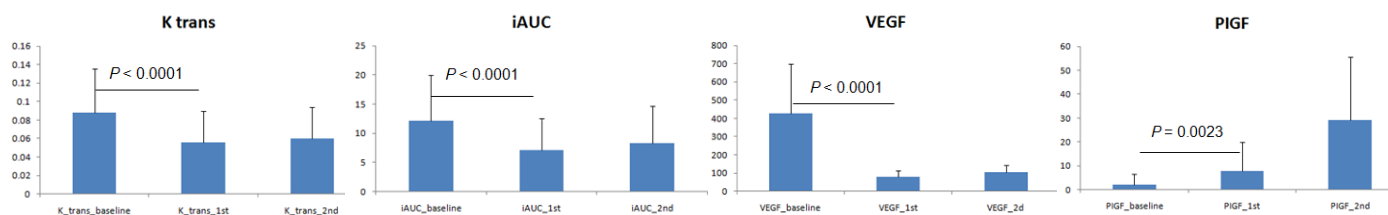


Figure 1 - Change of perfusion parameters of DCE-MRI and CAFs

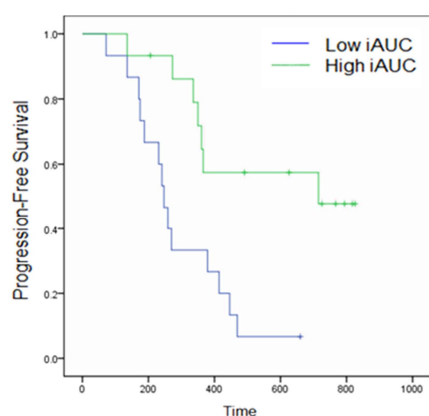


Figure 2 - Difference in PFS between high baseline  $i\text{AUC}_{60}$  group and low baseline  $i\text{AUC}_{60}$  group

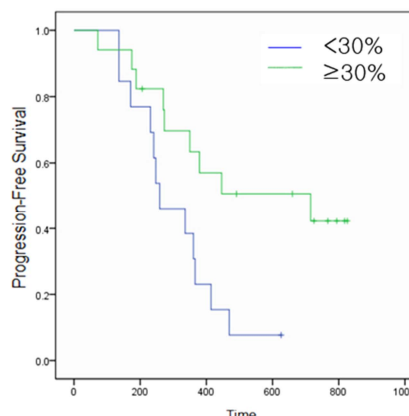


Figure 3 - Difference in PFS according to reduction of  $K^{\text{trans}}$  using 30% as a cutoff

## References

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